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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,297	02/13/2002	Masako Yajima	219451US0	3488

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,297	YAJIMA ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, STATUS OF THE APPLICATION AND CLAIMS

1. The amendment and remarks filed 10/29/04 are acknowledged, entered and considered. In view of Applicant's request the substitute specification has been entered, claims 1-8 have been canceled and claims 9-32 have been added. Claims 9-32 are now pending in the application. The objection to the specification, claims and abstract, the rejections under 35 U.S.C. 112, first paragraph and U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment and remarks filed 10/29/04. However, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Newly presented claims 9-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over JP 8-165248 (English Machine-Assisted Translation) taken with Elass-Rochard et al (Infection and Immunity, Vol. 66, No.2, pp. 486-491, February 1998).

Applicant's arguments filed 10/29/04 have been fully considered but they arte not persuasive. Applicant has argued that JP '248 discloses and suggests nothing regarding albumin exudation induced by LPS, and thus, JP '248 neither discloses nor suggests a method for alleviating 1) accumulation of body fluid containing albumin at the inflammatory site, 2) accumulation of albumin at the inflammatory site, or 3) decrease of albumin concentration in blood, by using human lactoferrin (hLf). Nor does JP '248 disclose or suggest anything with regard to alleviating 4) increased of blood neutrophils by using hLf. Applicant concludes by stating that the secondary reference of Elass-Rochard et al were carried out *in vitro*, and the mechanism concerning inflammation in the living body are very complicated and concludes by stating that the secondary reference discloses and suggests nothing to albumin exudation or increase of blood neutrophils, and thus nothing with regard to the presently claimed invention is unpersuasive.

Contrary to Applicant's arguments, the primary reference of JP '248 patent as discussed in the previous Office action teaches the administration of an effective amount of lactoferrin and its derivative as an active agent for suppressing inflammation caused by endotoxin LPS-derived from gram-negative bacteria, wherein the lactoferrin is administered in the form of oral agent, injection (e.g., parenterally), eye drop, or quasi-drug (e.g., mouthwash), cosmetic, food (e.g., chewing gum), etc. Depending on its use, the dosage ranges and mode of administration of the lactoferrin varies, for example, single dose of oral administration ranges from 1000 mg/kg to 4000 mg/kg or more; parenterally from 1 mg/kg to 50 mg/kg (See e.g., page 25) and as such overlaps with the dosage ranges claimed in claims 10-14, 16-20, 22-26 and 28-32 (i.e., 0.1 mg/kg to 1000 mg/kg). Thus, the reference clearly discloses the administration of lactoferrin as an active agent to suppress inflammation resulting in alleviating symptoms caused from LPS-induced inflammation due to acute inflammation or sepsis of the human by gram-negative bacteria (See e.g., pages 4, 5, 10, 13-15 and 25) as directed to claims 9-32.

Although, the reference of '248 patent does not teach the use of human-type lactoferrin for alleviating symptom from LPS-induced inflammation, however, on page 12, paragraph [0012], the '248 patent for example, suggests that the source of lactoferrin is not critical. Nevertheless, the secondary reference of Elass-Rochard et al discloses the use of human-type lactoferrin (hLf) *in vitro* to inhibit endotoxin interaction with CD14 by competition with LPS-binding protein (See e.g., the Title). On page 486, first paragraph, left column, the reference states that it is known LPS are potent

activators of the immune system. They stimulate host cells, mainly monocytes/macrophages and neutrophils, to produce endogenous mediators such as cytokines. On page 486, first paragraph, right column, the reference continues by stating that *in vivo*, hLf also regulates the release of TNF-α and protects mice against a lethal dose of *E. coli*. Thus, clearly showing that use of hLf increases blood neutrophils. On page 489, under discussion, the reference states that the ability of hLf to form complexes with LPS and thus to inhibit the LPS-induced release of cytokines by mononuclear phagocytes makes it a potentially important molecule in the inflammatory response. On page 490, last paragraph, the reference concludes by stating that Lf released from neutrophilic granules could neutralize the excess of LPS at the site of inflammation and protect the host against the excessive release of cytokines, and suggests that due to its high affinity for LPS, Lf could, *in vivo*, absorb small amounts of LPS. Further, *in vivo* studies are needed to investigate whether Lf could directly overcome the LBP-mediated activation of cells in the host and modulate the CD-14-independent LPS signal pathways.

With respect to the dosage ranges and mode of administrations, the ranges and mode of administration disclosed by the primary reference and claimed by Applicant overlap in scope as discussed above, and as such, the selection of the appropriate dosages and route of administration would have been *prima facie* obvious because where general conditions of claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges or situations by routine experimentation.

In regard to Applicant's allegation that the secondary reference discloses and suggests nothing to albumin exudation or increase of blood neutrophils, and thus nothing with regard to the presently claimed invention is unpersuasive. Contrary to Applicant's allegation, as acknowledged by Applicant on page 2, paragraph 2 in the instant specification, it is known in the art that during sepsis caused by gram-negative bacilli, decline in blood albumin concentration, decrease of lymphocytic leukocytes, and increase of neutrophil occur. Also, on page 4, Applicant acknowledges that bovine-type lactoferrin has been used to demonstrate an effect of alleviating various symptoms, which appear after infection. Thus, albumin exudation or increase of blood neutrophils at the inflammatory site, these are expected natural occurrence during inflammation whatever the cause of inflammation is. Therefore, in view of these and in view of the combined teachings of the prior art, particularly, the suggestion of the secondary reference of potential advantages of using hLf as discussed above, one of ordinary skill in the art would have been motivated at the time the invention was made to employ human-type lactoferrin for treatment or alleviating symptoms resulting from LPS-induced inflammation of human because of the expected species to species reaction. Use of lactoferrin from the same species (i.e., human lactoferrin to human) will decrease antigenicity and allergy induction, and as such, less toxicity occurs which will not trigger immunoreactions resulting from antigenicity.

Therefore, it is made obvious by the combined teachings of the prior art since the instant invention's methods of alleviating a symptom from LPS-induced inflammation by administering orally or parenterally hLf for the intended purposes of accumulating body

fluid containing albumin, accumulation of albumin, decrease of albumin concentration in blood, and increase of neutrophil in blood at the inflammatory sites, respectively; which fall within the scope of the prior art method and composition would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselet*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

The following is a new ground of objection necessitated by Applicant's amendments:

NEW MATTER OBJECTIONS TO THE SPECIFICATION

3. The amendment filed 10/29/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the addition of new matter on pages 2-4 and 9 by broadening the scope of the invention, change of the language and rearrangement of the specification by deletion and insertion. For example, there is no support in the originally filed disclosure on page 2, paragraph [0005] for the addition "**or bodily fluid**"; page 3, paragraph [0007] for the addition "**injection**"; page 4, paragraph [0011] for changing "**decrease of**" to –**maintain**--; and page 9, paragraph [0020] for addition "**injection**".

ACTION IS FINAL, NECESSITATED BY AMENDMENT

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272 0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
January 13, 2005